Department of Health and Human Services
National Institutes of Health
National Institute of Environmental Health Sciences
and
National Cancer Institute

Minutes of the Interagency Breast Cancer and Environmental Research Coordinating Committee Meeting

May 12–13, 2011

The Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC) convened for its third meeting on May 12, 2011, at 8:30 a.m. at the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina. Michele Forman, PhD, of the University of Texas, M.D. Anderson Cancer Center, served as Committee Chair.

The meeting was open to the public, and notice of the meeting was published in the *Federal Register*. The meeting agenda for the first day included opening remarks by Linda Birnbaum, Director of NIEHS, overviews of Subcommittee progress to date, and group discussion on global issues that have arisen in Subcommittee meetings. During the second day, the Committee resumed the discussion on global issues and the integration of the Subcommittee chapters into a cohesive report. During both days, Subcommittees met separately to continue work on their individual chapters. The agenda also included a 30-minute public comment session on May 13 beginning at 4:00 p.m.

Members Present
Christine Ambrosone, PhD
Janice Barlow
Beverly Canin
Sally Darney, PhD
Suzanne Fenton, PhD
Michele Forman, PhD
Michael Gould, PhD
Sandra Haslam, PhD
Ronda Henry-Tillman, MD, FACS
Karen Miller
Vivian Pinn, MD
Marcus Plescia, MD
Kenneth Portier, PhD
Jeanne Rizzo, RN
Gayle Vaday, PhD
Cheryl Walker, PhD
Sheila Zahm, ScD

Ex Officio Members Present
Dale Sandler, PhD

Neeraja Sathyamoorthy, PhD

NIH Staff Present
Linda Birnbaum, PhD, DABT, ATS
Jennifer Collins, MR
Gwen Collman, PhD
Caroline Dilworth, PhD
Christina Drew, PhD
Gary Ellison, PhD
Nonye Harvey, MPH
Christie Kaefer, MBA, RD
Laura McGuinn, MPH
Liam O'Fallon, MA
Kristianna Pettibone, PhD
Les Reinlib, PhD
Claudia Thompson, PhD
Deborah Winn, PhD

Other
Ernie Hood

I. WELCOME AND OPENING REMARKS

Dr. Linda Birnbaum (Director, NIEHS and National Toxicology Program) welcomed the Committee to NIEHS and its second in-person meeting, and she thanked Committee members and NIH staff for all of their hard work and continued commitment. Since the inaugural meeting, the IBCERCC has elected Dr. Michele Forman as Chair and formed three Subcommittees (see Dr. Forman's Introduction, below).

Dr. Birnbaum acknowledged the hours the Subcommittees and NIEHS and National Cancer Institute (NCI) staff have spent meeting and gathering the data needed to identify gaps and opportunities in research on breast cancer and the environment. She further reminded the Committee of her charges to address its mandate, to be bold and provocative, to consider all issues while being mindful of what is feasible, to effectively prioritize and identify partners, and to work together to produce a product that can be used by multiple stakeholders and ensure continued attention to the important research questions. Dr. Birnbaum closed her remarks by pledging the continued support of NIEHS and NCI staff in guiding the Committee's efforts, and committing to continuing the Committee's open forum for frank and honest discussion, where everyone's voice is valued. She further affirmed the importance of partnerships among breast cancer advocates, government program officials, and scientists from several disciplines to ensure the success of the Committee's work.

II. INTRODUCTION

Dr. Michele R. Forman (IBCERCC Chair, Professor Epidemiology, University of Texas, M.D. Anderson Cancer Center) began her introductory remarks by noting the Committee's broad

legislative mandate and highlighting the objectives and accomplishments of each IBCERCC Subcommittee.

- The State-of-the-Science Subcommittee (SOS; Chair, Michele Forman) aims to develop a comprehensive strategy and advise the National Institutes of Health (NIH) in the solicitation of applications for collaborative, transdisciplinary research, and outline key research questions and methodologies. In reviewing the literature, the SOS has developed two chapters, one focused on animal research and the other on human research. This Subcommittee also has discussed progress in breast cancer prevention, diagnosis, and treatment, and it has begun to identify gaps.

- The Research Process Subcommittee (RP; Chair, Michael Gould) aims to set research priorities, based on the work of the SOS; reduce redundancies across Federal and non-governmental organizations; develop a process for soliciting research and fostering collaborations; highlight issues of peer review; and identify appropriate models for agencies to work together. The RP has begun to develop two chapters, one on portfolio analysis and one on funding models, and it is considering chapters on research innovation, risk-reward, and new innovative models for research. The RP is also discussing research portfolios in breast cancer and the environment, as well as models for the conduct of research.

- The Research Translation, Dissemination, and Policy Implications Subcommittee (RTDPI; Chair, Jeanne Rizzo) aims to identify successful models and gaps in research translation and dissemination and recommend improvements, recommend policies to address translation and dissemination and precautionary public health policies supported by scientific evidence, identify methods to expand public participation in research translation and dissemination processes, and identify methods to more actively engage patient advocates and other stakeholders. This Subcommittee has established two subgroups. The subgroup focused on research translation and dissemination has identified seven potential chapters (sections), whereas the subgroup focused on policy implication has developed a chapter on why policy matters. The Policy Implications subgroup also has identified three other chapters (sections), is planning to establish a communications model with short- and long-term responses, and is discussing how to bridge communications across all the topics it is considering.

Dr. Forman suggested that this meeting be devoted to identifying barriers to each Subcommittee's tasks; additional resources, advisors, and Subcommittee members that might be needed to carry out each Subcommittee's task; and cross-cutting or global issues that challenge all Subcommittees. She cited the definitions of environment and innovation as examples of global issues. Dr. Forman also suggested that the IBCERCC explore what is known, identify potential audiences and their needs, and identify other potential areas where work is needed. She emphasized the need for the IBCERCC to provide clear, concise messages in its report and to prepare messages and materials for the dissemination of its findings.

Dr. Forman closed her remarks by providing an update on Institute of Medicine (IOM) activities. The IOM is completing its report on breast cancer and the environment. Several IBCERCC members have spoken with the IOM committee Chair and members of the IOM staff, and they are discussing the potential for two articles: one that will describe the objectives and tasks of

each report before the report is distributed; and one that will describe each report's findings and clarify any differences between reports.

III. OVERVIEW OF SUBCOMMITTEE PROGRESS TO DATE

Each Subcommittee Chair provided detailed reports of progress to date.

A. State-of-the-Science Subcommittee: Overview and Human Epidemiology Chapter

After re-introducing SOS members and reviewing objectives, Dr. Forman reported that the Subcommittee discussed the scope of the SOS report, particularly potential end points. The SOS initially focused on the incidence of breast cancer/mammary tumorigenesis, but subsequently expanded discussion to encompass recurrence, incidence of contralateral breast cancer, and survival. The Subcommittee also discussed exposures, which proved challenging because this endpoint depends on the definition of environment. The SOS thus narrowed its discussion to exposure to compounds like endocrine disruptors, as well as exposure to carcinogens that occur naturally or are created and concentrated by human activity. The Subcommittee has listed carcinogens related to breast cancer or mammary tumorigenesis, but it will also address effect modifiers and epidemiological confounders, including genes, the epigenome, psychosocial environment, lifestyle, and behavior.

The SOS has further divided into two groups. One, comprising Dr. Suzanne Fenton and Dr. Sandra Haslam, focuses on the state of the science in animal research, whereas the other, comprising Ms. Laura McGuinn, Dr. Christine Ambrosone, and Dr. Forman, focuses on human epidemiological research. Both subgroups started with summary articles, most of which were written in 2007, and assessed the reviews within those articles to determine the source of the reviews, source of funding, whether the reviews appeared in peer-reviewed journals, and whether the Subcommittee agreed with their findings. The SOS then turned to quantitative and qualitative studies published since 2007 and assessed them based on study design, sample size, methods (including data and biospecimen collections), laboratory analyses, data analyses, and confounders. The Subcommittee reviewed study results as well as study limitations and potential contributions.

Another subgroup, which included Ms. Janice Barlow, Dr. Heather Shaw, Dr. Neeraja Sathyamoorthy, and Dr. Forman, has also summarized progress in breast cancer prevention, diagnosis, and treatment. This subgroup has discussed potential criteria by which to judge a result as an advance, as well as whether progress in the entire field is a more appropriate focus. Dr. Forman presented several examples of potential advances and asked for input from the IBCERCC.

The SOS has developed two chapters, one devoted to animal research and the other devoted to human epidemiological studies. Both chapters begin with known risk factors and list known environmental exposures by the source of that information, but they go on to look for untested or unidentified exposures. Both chapters assess critical windows of susceptibility across the life course, as well as the kinetics of exposure. The chapters also address methodological challenges such as exposure validation, relevancy of models, and exposure assessments. Finally, both chapters have identified gaps and considered how to move forward in light of the interface and collaboration between animal and human research.

Dr. Forman then focused her presentation on the human epidemiology chapter, which begins by listing known risk factors such as age, age of menarche, first birth, and menopause. The chapter goes on to discuss known environmental exposures and critical windows of susceptibility across the life course; for example, evidence from animal research conducted by Russo et al. and her own research suggests that the a rodent of comparable age to an infant girl has her peak weight gain is associated with the age and onset of puberty. The age of peak weight gain can vary by *in utero* exposures and can differ for pre-eclamptic pregnancies compared with normotensive pregnancies. Other work has shown that the rate of linear growth between the ages of 2 and 7 years is associated with age of menarche and breast cancer risk. Dr. Forman also presented a slide from her work with the National Children's Study to emphasize that paradigms for development, windows of susceptibility, exposures, and terminology all vary and can thus confound the ability to define critical windows of susceptibility. Dr. Forman further pointed out that potential outcomes can occur many years after an exposure, further complicating the ability to define critical windows of susceptibility.

The epidemiology subgroup will examine the kinetics of exposure, for example the persistence, dosage, and inter- and intra-individual variation, and it will identify methodological challenges. For example, many exposure assessments contain a large amount of self-reported data that provides inconsistent findings, and the types of biospecimens collected and laboratory procedures vary. Coefficients of variation may be high, data on the handling and preparation of biospecimens are minimal, and exposure validation in humans is limited. There is no gold standard in terms of which biospecimen is best for which specific environmental exposure, there are no comparable approaches across studies, and data analysis has been hampered by sample size limitations, and inadequate adjustment for confounders. In addition, exposure validation requires knowledge of the critical period of exposure. Dr. Forman noted a few other gaps, such as the number of chemicals that have not been tested; limited to little or no data on breast cancer recurrence, metastasis, or survival; and limited understanding of what dictates a chemical's function as an estrogen or anti-estrogen.

Discussion

IBCERCC members suggested that the SOS get an idea of potential effects of untested chemicals by looking at work done by the Environmental Protection Agency (EPA) on structural activity relationships and identifying which of the untested chemicals share similar structures to those that have been tested. Members also suggested adding exposure (particularly pre-pubertal) to secondhand smoke, rare but high-risk genotypes such as *BRCA1*, and high-frequency but low-impact variants from genome-wide association studies (GWAS) to the list of known and accepted risk factors. In addition, Committee members suggested clarifying the type of hormone replacement therapy that is a known risk factor. The Subcommittee also was asked to consider adding developmental exposure to dioxins and DDT.

Dr. Ambrosone clarified that the first paragraph discussing environmental factors will focus first on known factors, then move to what has been examined, along with supporting evidence. The Subcommittee's aim is to briefly discuss known and accepted factors, then move on to discuss other potential factors. However, there was some concern that grouping these factors might be misleading. Ms. Beverly Canin noted that if the chapter grouped accepted factors with known ones, the SOS risked leaving these factors out of further assessments in the chapter. She

suggested that accepted factors and supporting evidence be noted, with additional language that there is still some uncertainty about these factors. Dr. Ambrosone added that the chapter would likely note factors that could explain up to half of breast cancer cases, then transition to factors that might explain the rest.

B. State-of-the-Science Subcommittee: Animal Chapter

Dr. Fenton began her presentation by cautioning that the SOS should specify that *developmental* exposures to environmental chemicals are a risk factor for breast cancer. She then reported that the animal studies subgroup has a first draft of its chapter that is now undergoing editing and formatting.

The animal subgroup's summary of the literature to date first assesses the utility of animal models in breast cancer research, particularly the most successful uses of rodent models, in testing carcinogenic substances. The subgroup defines a carcinogen, specifically noting the International Agency for Research on Cancer's (IARC) definition of human health hazard. The IARC definition states that unless there is evidence to show that rodent outcomes are not mechanistically related to human health, rodent outcomes should be assumed to be important for human health. This definition is somewhat different and less conservative than others, and the animal subgroup notes that it is based on science.

To further define the utility of animal models in breast cancer research, the animal chapter discusses similarities and differences between human and rodent mammary gland development, as well as differences between mice and rats, the potential advantages of each as a model, and similarities in hormone and growth factor regulation. The chapter also discusses the use of inbred versus outbred models, how that affects the variation within a study, and how it can mimic the variability found in the human population.

The chapter's next section addresses chemicals in the environment, because a lot of information is available in this area and some studies have been replicated, either in more than one species or more than one lab, to support a definitive answer. However, the tests available for Federal screening or testing guideline studies are poor and in the past have not required evaluation of the mammary gland. Thus, many of the chemicals are screened, but their effects on mammary gland tissue, development, and tumorigenesis are not known. Some changes have been made in the National Toxicology Program (NTP), such that mammary gland evaluations and developmental exposures have been added to each test. However, these changes are specific only to the NTP. The chapter discusses a movement to improve testing and the kinds of changes, such as a requirement for mammary gland evaluation, that are needed.

The animal chapter also discusses new lines of development beyond carcinogens. This section includes research on endocrine disruptors and the effects of changes in cyclicity, timing in puberty, and obesity on mammary gland development and late-life outcomes. Critical windows of development are also discussed. In contrast to human research, research in animal models has identified three critical periods: the fetal period of mammary blood development; puberty; and pregnancy. Because pregnancy and fetal development can overlap, the chapter distinguishes between effects on the mother and those on the offspring. Fetal programming is also discussed, because it affects both females and males, and the chapter notes that studies in multigenerational effects will need to be done at the Federal level, with input from academia. The chapter then lists

chemicals that have been shown to affect mammary gland development, as will be discussed in a paper by Rudel and colleagues in *Environmental Health Perspectives.*

The animal studies chapter discusses next steps, such as improved testing of chemicals, consideration of new mechanisms of exogenous hormone exposure, the need for reform of the Toxic Substances Control Act at the Federal level, an update of the NCI website on carcinogens, and the need for more research on reprogramming following early-life environmental exposures. Dr. Fenton added that the chapter should also discuss the use of cell lines in research on breast cancer or environmental effects on breast growth. She called for more interpretation and validation on the part of researchers to more effectively get at what might be happening in the body. The field should demand more relevancy of outcomes to ensure that research funding is spent wisely. The subgroup also called for more translational research and cited the NIEHS Breast Cancer and the Environment Research Program (BCERP) as a model. Dr. Fenton also called for more studies to bridge animal and epidemiological research, with more outreach to and input from patient advocates and community representatives.

Dr. Fenton highlighted other gaps, for both animal and human epidemiology studies and based on the work from the epidemiology and animal research teams, and asked for input from the Committee:

- The need to better define appropriate species and strains for interpretable research. For example, research is still being done in the Sprague-Dawley rat, even though it is not a good model endocrinologically.
- The need to include mammary end points in Federally funded screening and testing guideline studies, which could aid in defining critical windows of development.
- The need to require testing for grandfathered and new chemicals in the marketplace.
- The need to define alterations in cell types or signaling events in animals, three-dimensional models, or cell models. Such a definition can aid in translating animal findings to human health.
- The need for a better understanding of the physical, chemical, hormonal, and lifestyle exposures that are detrimental to development and could increase lifetime risk for breast cancer (humans and animals).
- The need to identify and track exposures in a time-specific way and to develop time-specific biomarkers (humans and animals).
- The need to better understand gene-environment interactions (humans and animals).
- The need for more research on multiple and mixed exposures (humans and animals).
- The need for a clear definition of mammographic density (humans).
- The need for a strategy to study groups that are at high risk based on their genetic background, their environmental exposures, or both (humans).
- The need to understand when a chemical acts as an anti-estrogen or an estrogen (humans).

- The need for more research on other hormones that might increase risk for breast cancer (humans).
- The need to identify and use optimal laboratory procedures across studies to ensure comparability (humans).
- The need to determine when there are enough data to translate findings to action (animals and humans).

Discussion

The IBCERCC agreed that consistent findings from two or more observational studies, across species, or across laboratories were needed before findings can be translated into action. Committee members also agreed that actions should be taken based on observational studies, because randomized clinical trials are unethical in humans or animals.

Dr. Deborah Winn suggested a separate section devoted to mechanisms underlying the links between environmental exposures and risk for breast cancer. Such a section could include the kinetics of exposure, the genetic or epigenetic effects of that exposure, and the metabolism of a chemical once it enters the body. Dr. Winn further suggested that such a section could provide a conceptual framework to distinguish between chemicals that likely behave as carcinogens and those that are more likely to be promoters.

Dr. Gould suggested that the subgroup's comments on how testing is interpreted and regulated should be brought together in a section near the end of the chapter. This section could tie into the gaps—for example, better animal models and improved understanding of mechanisms—and serve as a transition into a discussion of the current state of and potential improvements in regulation. Ms. Rizzo indicated that the RTDPI has a section addressing this issue in their chapter. Dr. Sally Darney added that ways to examine pathways of toxicity and integrate that information present a challenge across all toxicology. The EPA, NIEHS, NIH, and U.S. Food and Drug Administration (FDA) have formed a consortium to look at this issue, but they do not focus on breast cancer. She noted the complexity of breast cancer when considering pathways, and she noted that because of this complexity, many are not thinking about breast cancer and pathways of exposure. However, she suggested that IBCERCC could encourage the consortium to add such a focus.

Dr. Neeraja Sathyamoorthy noted that an NCI grantee at the University of California, San Francisco is using a combination of in vivo and in vitro structural, genetic, molecular and functional analyses of human tissue to identify candidate markers that link high breast density with an increased risk for breast cancer.

Dr. Ambrosone noted that in the laboratory, animals are exposed to one or more carcinogens but that humans are exposed to many things that increase or decrease risk. She recommended caution when discussing the relevance of animal models to human cancer and public health.

C. Research Process Subcommittee

After acknowledging the members of the RP, Dr. Gould reviewed and elaborated on the objectives of this Subcommittee:

- Set research priorities. The priority-setting work of the RP will be based on the work of the SOS; thus the RP plans to work with the SOS, as well as with advocacy groups, to understand gaps and determine how to move forward.
- Decrease redundancies. Some redundancy, such as repeating a study to confirm results, is useful. Thus the RP would focus on reducing non-productive redundancies.
- Develop a process for soliciting research. Normally, academic scientists submit investigator-initiated applications, but many applications focused on issues raised by Dr. Fenton would not be funded, even absent budgetary constraints.
- Foster collaborations. Despite the potential benefit of collaboration, Dr. Gould called for a balance between collaboration and individual ideas. The RP will work with the RTDPI in developing ways to foster collaborations.
- Highlight peer-review issues. Without good peer review, good science will be impossible. To increase the likelihood of obtaining funding for the types of studies suggested by the SOS, requests for applications (RFAs) and other mechanisms will be needed to guide peer review.
- Identify appropriate models for agencies to work together. Dr. Gould pointed out that the current models are not working; if they were, there would be more advances in breast cancer than are seen at present.

Dr. Gould reviewed the Subcommittee's approach, which aimed first to conduct an analysis of the Federal research budget and an investigation of programs at the Federal, State, and non-profit levels to identify funding for breast cancer, the source of funding, and overlaps and gaps in funding. The Subcommittee has developed outlines for two chapters: one devoted to portfolio analysis, and another devoted to funding models. The Subcommittee also has developed a preliminary list of additional topics, including innovation, risk and reward, a role for advocates in the research process, single versus multiple principal investigators, and how to fund emerging science. Cross-cutting issues, such as team-based science, well-defined problems, and concrete and attainable goals, also have been discussed. Dr. Gould invited input from the IBCERCC on other potential topics.

Following an introduction, the portfolio analysis chapter will discuss methods for identifying relevant funded research and, more importantly, transparency in funding. The chapter will then summarize the RP's findings, discussions, and recommendations. An initial analysis of the NIH and Department of Defense (DoD) portfolios has been conducted. NIH, the largest funder of breast cancer research, offers a tool, called RePORTER, which allows users to search a repository of NIH-funded research projects and to access publications and patents arising from these projects. Although this tool is useful, there is room for improvement. For example, a lot of what is found in RePORTER depends on how grants are coded, so caution is needed in interpreting the proportion of the NIH budget devoted to breast cancer research.

A search for breast cancer yields about 3,000 unique hits from the RePORTER system. A small number of these are contracts, another 171 may have been miscoded and are not relevant to breast cancer, and almost 200 are primarily research center or intramural projects. An examination of the remaining hits reveals that the bulk of funding goes toward research, be it R01s, program projects, or intramural research. A further breakdown of research funding shows

that the bulk of money supporting breast cancer research comes from NCI, followed by NIEHS. However, it is difficult to determine how much research money funds projects focused on breast cancer and the environment. Like other Federal agencies, NCI uses the Common Scientific Outline, which lists seven broad areas of scientific interest in cancer research: biology; etiology; prevention; early detection, diagnosis, and prognosis; treatment; cancer control, survivorship, and outcomes research; and scientific model systems. About 16% of research funding goes toward etiology, but etiology has been broadly defined and is not coded in the RePORTER system. Thus, out of the 16% of grants focused on etiology, only a small fraction focus on the topics highlighted by the SOS.

Dr. Gould also presented a list of environment-related terms appearing in the portfolio, with the understanding that the IBCERCC is still trying to define "environment." Several projects are related to occupational, clinical, lifestyle, and psychosocial terms, as well as specific chemicals, hormones, genes, radiation, oxidative stress, and inflammation.

The DoD Breast Cancer Program appears to fund more innovative and riskier breast cancer research. In addition, the Program manages grant data using an electronic grants system, and it uses two coding systems, the Common Scientific Outline and an internal system, to code grants. When investigators apply for funding, they must submit identifiers for both systems. Although accuracy in coding is still an issue, DoD often recodes grants. With respect to the environment, the DoD coding systems use common scientific terms such as exogenous factors (environmental chemicals) and interactions between genes and the environment. The system also codes for common scientific interventions for prevention, primary prevention, biobehavioral sciences, and epidemiology.

Of a total of 1,850 grants awarded from fiscal years 2005 through 2010, 135, or 7.3%, had environmental codes. It is likely the NIH portfolio analysis will yield similar numbers. Dr. Gould cautioned that the IBCERCC, the community, and Congress must decide how important the issue of breast cancer and the environment is, what is an acceptable or adequate proportion of the research portfolio devoted to it, and what sacrifices in other areas of research should be made, if necessary.

With the assistance of NIH staff, the RP has begun to develop an outline for the chapter on Federal research programs and funding models. The chapter will include an introduction, followed by a look at existing programs, other models for research collaborations, a discussion, and recommendations. Existing Federal models include research consortia such as BCERP, research collaborations such as the Centers for Children's Environmental Health and Disease Prevention Research, research networks such as the Cancer Genome Atlas, research centers funding, innovative competition awards such as the DoD Idea Awards or the EPA P3 Grants to College Teams for Environmental Innovation, and innovative scholar awards to train the next generation of scientists.

Funding programs are also available from the States, such as the California Breast Cancer Research Program, the Pennsylvania Breast and Cervical Cancer Research Fund, and the Illinois Women's Health Mini-Grant Program, and several of these programs can serve as models for ways to encourage innovation. Another funding program, an Accelerated Research Collaboration supported by the Myelin Repair Foundation, is putting 100% of its funding into a high-risk, high-

reward project to explore a cure for multiple sclerosis. The program is structured to support collaboration not only between investigators, but also between academia and industry. Other potential models are business models, which often include milestones and some level of accountability. The RP is also looking at models that support projects focused on ideas arising from think tanks and the National Science Foundation (NSF) Ideas Lab.

The RP is still finishing the portfolio analysis and determining how much detail to add to the chapter outlines. The Subcommittee plans to analyze research gaps, to identify ways to address them and remove non-productive overlaps, and to determine how to further foster interagency collaboration. The RP also is considering outlines for four more sections devoted to research innovation, risk and reward, identifying and filling research gaps, and new and innovative models (incorporating advocates) for research.

Dr. Gould acknowledged the support of NIH staff in the Subcommittee's portfolio analysis. However, he called for additional and other types of staff support as the RP moves from outlines to fully written chapters. He also noted the need for help from other Subcommittees to identify and address research gaps, the need to incorporate advocates in developing research models, the need for an action plan to implement and respond to findings from the IBCERCC's reports, and the need for more materials and references to aid in the RP's chapter writing and continued investigation of funding models. Within the next 3 to 4 months, the RP aims to draft its portfolio analysis and funding models chapter, decide on additional chapters, and begin discussions on overall analysis and recommendations.

Discussion

In response to questions from Dr. Cheryl Walker, Dr. Gould clarified that the final report would likely discuss gaps highlighted by the SOS and innovative models suggested by the RP to address those gaps. More discussion is needed to identify such models and where to invest in the future.

Dr. Sathyamoorthy responded to a question raised by Dr. Gould during his presentation regarding National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) support of breast cancer research. NIDDK is interested in steroid hormones and is thus supporting basic biology projects to understand hormone action. Such projects could have implications for cancers of the breast and prostate.

Dr. Fenton noted that the Eunice Kennedy Shriver National Institute of Child Health and Human Development has held a variety of meetings on how to improve its research efforts and where the Institute should go during the next 10 years. She invited IBCERCC members to read and make suggestions on the white paper developed by the work group on the environment. Obesity and time of puberty, which were highlighted by the SOS as factors that could affect breast cancer risk, were mentioned at this work group meeting, and the Committee can push for a focus on the environment and early-stage changes. Dr. Fenton called on the Committee to support these types of efforts, which could form a bridge for the IBCERCC. Dr. Gould agreed on the need for cross-fertilization, noting the disconnects among Institutes, Federal agencies, and academia and how little each sector knows about the work the other sectors are doing with respect to academic,

regulatory, and testing research. The National Children's Study is another area where the Committee could push for a focus on environmental issues.

The Committee further discussed funding models. Committee members suggested that the RP's gaps analysis should assess how much is spent in different funding models and determine whether funds should be redistributed toward more productive models. For example, fostering multidisciplinary collaboration might be better served by centers and networks than by individual R01s. Dr. Birnbaum suggested that in light of declining budgets, approaches should be found to balance an emphasis on productive funding models with investigators' desire to continue R01 support. Dr. Dale Sandler also suggested that the RP assess where funding is targeted with respect to research infrastructure.

Metrics and evaluation were also discussed. Dr. Haslam pointed out that metrics should be defined to evaluate success and guide the Subcommittee's recommendations. Possible metrics include the number of investigators working in the field of breast cancer and the environment, whether investigators feel this field is a vibrant area of future research, how willing investigators are to submit applications, and the success rates of those applications over time. Although those metrics cannot be assessed readily through databases, they do point toward growth and development of the field. Dr. Gould noted that success or failure could be self-fulfilling. For example, if study sections seldom look at toxicology, those applications are less successful, and recruiting more investigators into the field is more difficult.

Ms. Canin mentioned that DoD does not specify or solicit applications according to categories in the Common Scientific Outline or its internal system. Instead, the Department uses mechanisms such as Idea Awards, the multidisciplinary Era of Hope awards, and awards focused on innovation to solicit applications. Dr. Vaday added that although most, if not all applications for the DoD Breast Cancer Research Program focus on prevention, there has been some discussion about directing or soliciting applications more specifically, for example to environmental factors. However, the Department has usually chosen to keep its mechanisms broad, based partly on recommendations from the IOM at the time the program was initiated.

D. Research Translation, Dissemination, and Policy Implications Subcommittee

After reintroducing the members of the RTDPI and restating the Subcommittee's objectives, Ms. Rizzo reported that the Subcommittee has divided into two teams and identified some areas of potential overlap with the RP. The RTDPI also has identified its stakeholders as individuals, communities, clinicians, study participants, researchers and scientists, legislative policymakers, and various types of agencies. She then turned the presentation over to the representatives from each team.

Ms. Canin reported that Team 1 has reviewed the history of community involvement in breast cancer research since the 1970s, when breast cancer activism emerged as a core component of the feminist movement. The team has reviewed examples of community-based studies done on Long Island, on Cape Cod, and in Marin County and some literature related to consumer involvement in the breast cancer and environment movement. The team also has interviewed several authors and experts: Geoffrey Kabat, author of *Hyping Health Risks: Environmental Hazards in Daily Life and the Science of Epidemiology*; Sabrina McCormick, author of *No Family History: The Environmental Links to Breast Cancer*; Barbara Ley, author of *From Pink*

to Green: Disease Prevention and the Environmental Breast Cancer Movement, and Ann Hernick, author of *Sharing Unexpected Biomarker Results with Study Participants*. Ms. Canin also reported that the team has developed a list of key research translation models, which were outlined in a handout given to IBCERCC members, and created working definitions for research translation and research dissemination:

Research translation is the transfer of scientific discoveries from laboratory, clinical, or population studies into effective interventions at the population level, quantifying and integrating the best new methods and technologies across disciplines, and creating tools for high public health impact. It must provide usable data and information for multiple audiences and multiple uses—scientific, regulatory, public policy formation, public communication—to improve health by reducing breast cancer incidence, morbidity, and mortality. Collaboration between research producers and research consumers is critical in this translational approach.

Research dissemination is the targeted distribution of evidence-based research findings intended to influence clinicians and other health professionals, patients, program planners, and policymakers in ways that ultimately reduce the breast cancer burden in society. Effective dissemination is an interactive exchange between researchers and those with a vested interest in the research. Effective communication is oriented toward the needs of the user, includes various dissemination methods, and draws upon existing resources, relationships, and networks as much as possible.

Ms. Canin invited IBCERCC members to further discuss these definitions. She added that the team did not feel that the definition of research dissemination covers everyone or touches upon the average consumer. Some team members feel that individuals have a vested interest in research on breast cancer and the environment, whether those individuals recognize that interest. The Breast Cancer and Environment Research Program (BCERP), Partnerships in Prevention, Partnerships for Environmental Public Health, the California Breast Cancer Research Program, pediatric environmental health specialty units, the NCI Consumer Advocates in Research and Related Activities Program, and Image Gently were some of the research modelsmodules listed as applicable to breast cancer and the environment.

Team 1 is now reviewing the patient advocacy literature, particularly with respect to the role of health care providers, as well as literature on community-based participatory research, health literacy and plain language models, and strategies for communicating findings to diverse audiences. Ms. Canin noted *The International Journal of Community-based Research* and the concept of a "Science Shop," which brings scientists together with consumers, as examples. In addition, the team is reviewing models of research translation to identify needs and potential barriers. One barrier Ms. Canin highlighted is the overlap between translation and dissemination, which is often not acknowledged in descriptions of these activities. The team identified a number of other needs:

- The need to expand translation and dissemination efforts in existing research, perhaps as required by funders, evaluated in peer review, and monitored in progress reports.
- A mechanism for a fast track, so that issues of high impact or high public health concern can be addressed immediately.

- Toolkits for translating and disseminating science to the public, advocates, and the media.
- An evaluation of the role of communication strategists who work with scientists to communicate research results.

Team 1 also intends to address additional objectives, such as recommendations to improve translation and dissemination of breast cancer and the environment to maximize public health impact and recommendations for public policy to address such translation and dissemination.

Dr. Marcus Plescia reported on the activities of Team 2, which is focused more on policy implications and communication. Team 2 has reviewed recent national reports addressing potential toxins and cancer. Although these reports are fairly broad and not specific to breast cancer, Dr. Plescia noted that overall themes in some of these reports apply to the IBCERCC's discussions and that the team's chapter might allude to specific recommendations. One such example is that of the President's Cancer Panel 2008-2009 Annual Report, which emphasizes the need to shift toward a prevention-oriented approach and makes recommendations regarding exposures to radiation, particularly in the medical setting. Another is the National Conversation on Public Health and Chemical Exposures, which recommends, among other things, a strengthening of the public's ability to participate in environmental health decision making and of the public health provider workforce's capacity to address other issues outlined in the report. Team 2 proposes that its chapter reiterate areas of particular importance, then comment on a possible national registry of databases, the public's right to know, and public access to data. The team disseminated handouts outlining other ideas. However, Dr. Plescia noted that the RTDPI will look to the other Subcommittees for guidance on recommendations and areas of emphasis, which will depend on the IBCERCC's assessment of the science.

Team 2 also has considered potential issues around communication, and it has consulted with Dr. Galen Cole, Associate Director of Communications at the Centers for Disease Control and Prevention. The team has noted that the area of breast cancer and the environment, as well as its science, remains controversial and that communicating about it remains tricky. Yet moments of crisis will require information to be disseminated early. The tension between the care needed in communication overall and the need to get focused information out early during crises is a core issue identified by Team 2. Other preliminary recommendations by the team include:

- Identifying methods to more effectively engage advocates and practitioners in communications about emerging environmental risks.
- Preparing a communications toolkit to guide the formulation and testing of messages.
- Clearly articulating a research and evaluation agenda for communicating science related to breast cancer and the environment.
- Developing clearly defined communications plans across government agencies.
- Increasing governmental agency access to social media interfaces.
- Broadening outreach into the "pink ribbon side" of the breast cancer advocacy network.

Dr. Plescia concluded his remarks by highlighting questions for other Subcommittees and by emphasizing that the work of the RTDPI will depend on what comes out of those Subcommittees.

Discussion

IBCERCC members noted the desire of breast cancer advocates to publicize research findings and the need for researchers to share actionable information. For example, demand has exceeded capacity for environmental health training seminars conducted by Commonweal and the California Breast Cancer Research Program. Another communication issue raised by committee members is the "distal" nature of breast cancer risk. Ms. Janice Barlow noted that mothers might not always prioritize information about *in utero* or pubertal exposures, because breast cancer risk is distal when other concerns are more immediate. Ms. Rizzo suggested that communication strategies might make a difference; for example, mothers responded immediately on a bill regarding toxic toys. Outreach to health care providers, particularly obstetricians-gynecologists, is another communications need. Recommendations for programs and interaction between scientists and the media, such that the media learns how to interpret data and avoid making all results newsworthy, were also suggested. Ms. Rizzo acknowledged the Society of Environmental Journalists and suggested that the recommendation on toolkits emphasize the need to provide talking points and pitch science stories in a way that will grab journalists' attention.

Dr. Birnbaum raised the issue of the economics associated with health policy. She specifically noted the need to educate the public about breast cancer-associated costs that could be reduced if certain exposures were avoided. Dr. Birnbaum also directed the Committee's attention to *Health Affairs*, which recently published its first issue regarding health affairs and the environment. Although this issue does not specifically address breast cancer, it does provide several examples of health economics. Dr. Birnbaum noted that this journal is read by policy makers and that the Committee should consider ways to increase awareness and knowledge among policy makers.

Ms. Barlow suggested that the RTDPI also look at models in other countries regarding research and ways to involve community advocates. In addition, BCERP serves as a model for including advocates in research design, contributing limited funding to the advocacy community, and providing opportunities for meetings where scientists and advocates can collaborate and share findings. However, more dialogue is needed between scientists and advocates during the research process. For example, when and how to provide the public with information to reduce or eliminate environmental exposure at the end of a study is still a point of strong disagreement.

IBCERCC members suggested that prevention and the individual or personalized level be added to the RTDPI's definition of research translation.

IV. GROUP DISCUSSION OF GLOBAL ISSUES

Committee members discussed global issues that have implications for their work and that have arisen during Subcommittee meetings. The overriding issues that are challenging all Subcommittees include definitions of terms like "environment," "innovation," "high risk, high reward," as well as metrics for evaluating success. Although the agenda called for a presentation on integrating Subcommittee products and chapters into a cohesive report on the morning of the

second day, Dr. Forman did not consider the Committee ready to discuss integration. Instead, this time was spent discussing issues raised during the previous day's discussion on global issues. The following summarizes the group discussion about global issues on both days of the meeting.

A. Definition of the Environment and Environmental Influences

Dr. Forman presented a possible statement defining the environment; this statement was excerpted from one made by Dr. Sheila Newton (NIEHS) in September 2010. The IBCERCC further revised the statement to say that "the environment includes all of the surroundings and influences on living organisms." Dr. Forman invited the Subcommittees to consider this definition further during their breakout discussions.

The general statement defining the environment will be followed by a statement that the IBCERCC report will focus on specific environmental influences selected by the Committee. After reviewing Dr. Gould's list of potential influences, Committee members suggested that they focus on and provide rationales for the following influences:

- Consumer products (including cosmetics, household products), specifically the synthetic and naturally occurring chemicals contained therein.
- Lifestyle factors, including diet, obesity, and alcohol use.
- Endogenous hormones.
- Emerging environmental agents, for example nanoparticles.

The Committee noted that the environment encompasses all these influences and suggested that the report include a statement about the complexity of environmental influence. For example, specific environmental influences can play different roles at different times and across different breast cancer subtypes. Moreover, although the few women who have highly penetrant situations (for example, *BRCA1/2*) remain a concern, it is likely that in the general public, many environmental influences will be of low penetrance and interact. It is unlikely that any one chemical will be the sole explanation for breast cancer risk. Committee members therefore emphasized possible interactions among environmental factors. Some also noted the importance of differential susceptibilities and personalized medicine.

There was also discussion about the inclusion of "endogenous hormones" as a potential influence. One member pointed out that the Common Scientific Outline code focuses specifically on the interactions of gene polymorphisms with exogenous and endogenous factors and that the Committee would have to tease out endogenous factors. Another member pointed out that known mechanisms of endocrine disruption directly influence endogenous hormone levels and can have profound effects. Yet other Committee members noted findings that serum hormone levels do not appear to correlate with breast cancer or other end points of interest.

Several IBCERCC members suggested that the introductory statements in the report should note that the Committee is focusing on broad categories of influences (for example, physical, chemical, lifestyle or behavioral, response to stress). These categories could be presented in a graphic at the beginning of a report, similar to a model presented by Dr. Marie Lynn Miranda, of

the Duke Children's Center. Ms. Canin also reminded committee members that this report will have multiple audiences and that scientific terms need to be defined.

Dr. Forman asked that during the breakout discussions, the Subcommittees consider further how to prioritize influences and develop rationales for that prioritization.

B. Innovation

IBCERCC members considered ways to define research innovation, and recognized that innovation can be defined at several levels. Technological innovation, or the use of new technology to advance the field, is a fairly simplistic definition, and could include methodological advances in exposure assessment and validation. However, what is meant by "advancing the field" can be defined in several ways, depending on the scientific discipline or study. Dr. Shelia Zahm pointed out that a field can move forward by definitively answering a question using an old method.

Dr. Kenneth Portier suggested that innovative ideas represent a significant jump, rather than an incremental step, and change paradigms. One example, as noted by Ms. Karen Miller, is a shift from thinking about "bench to bedside" to thinking about "bench to trench," or getting information to the individuals needed to implement it. Another example, cited by Ms. Rizzo, is a paper by Woodruff and Sutton that provides a guide for evidence-based medicine to bridge the gap between clinical and environmental health science. Other Committee members suggested that an idea should involve a valid approach and generate usable data to be considered innovative. Ms. Rizzo cited a paper by Dr. Birnbaum, who concluded that an environmental health strategy must integrate the best new methods and technologies to provide usable data and information for multiple audiences. Dr. Fenton referenced atrazine and breast cancer, which has been beset by poor epidemiological and animal studies, as well as by inappropriate extrapolation from cell studies to human breast cancer, and is thus a point of confusion. She added that potential environmental influences should be validated across strains or species of animal. Dr. Portier also emphasized solid science, noting that the wrong message can come from bad science or from good science extrapolated the wrong way. Committee members agreed that a definition of innovation should distinguish true innovation from mere gimmicks.

On the second day of the meeting, Dr. Forman asked Committee members to provide examples of innovation, based on perspectives from their Subcommittees, with the goal of developing an overall definition that could be added to the introduction of the report. She noted that the Breast Cancer and the Environmental Research Act mentions innovation several times but that this term could be defined differently from different perspectives. She added that the previous day's discussion considered innovation primarily from the perspective of the study section.

Committee members noted that innovation is most relevant in the research process and that innovation is often mentioned now because of the lack of progress in the field of breast cancer and the environment. They defined innovative ideas as those that have an impact and exert changes in the knowledge that is gained or in the approaches investigators use to gain that knowledge. Innovation was defined as "tackling new questions," "unique," "paradigm-shifting," "radical," "high-risk," and "non-incremental." Dr. Gwen Collman indicated that innovation is often built into the questions generated by multidisciplinary groups as they apply their collective wisdom to a research problem. Ms. Rizzo noted that innovative questions often arise with

emerging scientific opportunities, where scientists have traditionally waited for more data. Dr. Sathyamoorthy added that some NIH programs, such as the NCI Awards to Promote Research Collaborations, are innovative because they require collaboration between two or more investigators who come from different disciplines and might not have worked together before.

Innovation was also described as developing a new language. Ms. Miller pointed out that language differs across agencies, across disciplines, and between scientists and the public. She suggested that agencies work together to develop a new language with key phrases that everyone, including the public, understands. Such a task could facilitate the standardization of message delivery and the communication of new discoveries and emerging opportunities.

Some Committee members suggested that innovation itself could be used as a metric for continued investment. Projects touted as innovative could be assessed at the end of a funding period to determine whether they have had an impact. If so, then the projects would be eligible for renewed funding. Committee members acknowledged that whether an application is deemed innovative often depends on who is reviewing the application, and they therefore suggested that both objective and subjective criteria for innovation be established.

Dr. Gould suggested a radical shift in funding models. At present, all funding decisions are based on applications' average priority scores. Dr. Gould suggested a model in which 90 percent of funds are still awarded in this manner but the remainder would be awarded based on the degree of variance in an application's scores. He pointed out that innovative ideas often receive a wider range of scores in study section, because some reviewers will be more hesitant whereas others will be excited by the idea. This funding model would go beyond the current process whereby Institutes pick up some innovative, high-risk, high-reward projects with discretionary funding. Dr. Gould acknowledged that there are many reasons for variance, but he suggested an experiment where wide variance in overall or innovation scores at least triggers a closer look at the application by NIH.

The Committee also discussed innovative changes in research infrastructure, where resources are allocated in a way that encourages bridge-building among Institutes to build systems needed by researchers. Institutes and other agencies also can be innovative if they integrate or collaborate on ways to solicit research. Innovation in methodological research also was suggested. Such research could address basic questions reviewers often dismiss because they think data already exist.

Dr. Zahm cautioned that innovation could be present not only in scientific approaches, but also in the type of research question. The Committee agreed to note in the report that many fundamental research questions on breast cancer and the environment will not be innovative but still should be addressed. Committee members cautioned against using innovation as a sole criterion in judging applications or dismissing important ideas simply because they are not innovative. Other Committee members suggested that although the introduction of the report will include an overall definition of innovation, each section or chapter should also define innovation as it relates to that chapter. Dr. Winn will incorporate this discussion into a draft discussion of innovation.

C. High Risk, High Reward

As noted by Drs. Gould and Haslam, high risk and high reward need more definition. It is not clear how high a risk is acceptable, and metrics to evaluate success rarely clarify what the reward is. Reviewers for the DoD breast cancer program view high-risk-high-reward as a strong idea an investigator has, even though he or she might have little to no preliminary data to support it. DoD acknowledges the risk that the idea might fail, but it also expects that the research will generate a larger outcome. However, it is not clear how much risk can be taken when research is closer to the clinic, as could be the case with research on breast cancer and the environment.

Committee members cited the Myelin Repair Foundation's Accelerated Research Collaboration and the NCI Genome Anatomy Project as examples of high-cost, high-reward projects. However, both projects are costly, and in general, cost is a challenge for high-risk, high-reward studies. For example, complex mixture studies are often done in animal models, and high-risk, high-reward studies in animal models often are not funded because the costs appear to be prohibitive. Dr. Portier suggested that a definition for high-risk-high-reward should include an acknowledgement of the risk that nothing will be learned from the idea, which could be problematic with ideas that carry a high financial cost.

Peer review also is cited as a barrier to high-risk, high-reward projects. Ms. Canin noted that peer reviewers might not have been trained to determine when a study fits a valid model for high-risk, high-reward projects. She suggested that the Committee recommend that peer reviewers be cognizant of and enforce whatever models or definitions are agreed upon as high risk, high reward. Dr. Collman also reminded the Committee to think beyond investigator-initiated applications and peer review and consider roles for high-risk, high-reward projects within intramural programs and infrastructure building. The creation of new technology that provides infrastructure that yields data and facilitates various kinds of discovery might not successfully pass peer review, but it can be achieved by an agency or a collaboration of agencies. The NIH Chemical Genome Center was cited as an example.

D. Metrics for Evaluating Success

In discussing the purpose of its report, the Committee considered short-, intermediate-, and long-term goals. Short-term goals include publication of the IBCERCC report and meeting its objectives, and intermediate goals include making an impact on how federal research on breast cancer and environmental factors is funded and managed. The RTDPI might also develop a set of intervention messages, based on the current science, in the near- and mid-term. A number of possible long-term goals were mentioned: the reduction of breast cancer incidence from environmental influences, research that provides a scientific basis for public policy and prevention guidelines, and prevention through increased understanding of the interface between environmental exposures and windows of susceptibility. This increase in understanding can aid in the identification of interventions that can work at earlier stages to prevent development of breast cancer. The ability to provide definitive answers on putative environmental factors was also suggested as a goal. Such answers can lend more credibility to prevention programs focused on those factors.

Dr. Portier cautioned that research programs should have an external and internal goal. He pointed out that many agencies do not specify objectives for their research programs. Thus external evaluators cannot judge the programs' success. He suggested that the Committee's

report recommend that all agencies have clearly stated goals and specifications in each of their research programs on breast cancer and the environment. Dr. Portier added that program goals should explicitly state a link to public expectations, which generally focus on how research improves lives.

Suggested metrics to evaluate success included the degree to which an idea or study stimulated new kinds of research, as measured possibly by citation counts and the number of physicians and health care providers who talk more proactively about a potential environmental trigger.

Committee members raised a number of other considerations related to the report under development:

- The definition of research translation should cite *measurable* reductions in breast cancer incidence, morbidity, and mortality as a goal. Stating that reductions should be measurable will facilitate use of metrics to evaluate success.
- The report should discuss the progress that has been made in research on breast cancer and the environment in the past 30 years of funding in this field. However, what constitutes an advance and progress remains to be defined.
- Prevention should be emphasized in the report.
- Although goal-driven research will be useful, the research portfolio should balance this with exploratory research.
- It is not clear how definitive research findings must be before policy and environmental exposures change. The threshold can differ for scientists and advocates; thus these groups must work together to set criteria for moving forward on conclusions. The report also can address this issue while discussing the Committee's conclusions.

On the second day of the meeting, the Committee agreed that short-, intermediate-, and long-term metrics should be specified in the report and that these metrics should be considered as recommendations are made. Some members suggested that short-term metrics would include completion of the report and its recommendations, whereas others felt the clock for short-term metrics should begin upon delivery of the report. All members agreed on the short-term goal to establish a monitoring system to assess the effectiveness of recommendations and responses to the report. They suggested, for example, a short-term goal of implementing an interagency process with an initial agenda, then monitoring to see whether agencies meet, whether they review the report, and how they respond. Members also considered recommending that the IBCERCC remain in place to monitor short-term goals. Dr. Gould suggested a process where an audit is done to determine whether grants coded as relevant to breast cancer and the environment have been coded correctly, and the coding system be changed or abolished in favor of text mining. Such a task will allow funding distribution to be followed more accurately. However, Dr. Gould and others cautioned that investigators and institutions could manipulate the coding system.

Publications and products arising from a research project were suggested as intermediate-term metrics. The number of investigators or groups who include a plan for translating and disseminating research results in their applications, rather than consider them only at the last

minute, was also suggested. The bulk of discussion on intermediate-term goals and metrics, however, focused on funding mechanisms and peer review. Some members suggested an evaluation of dollars committed toward research on breast cancer and the environment and toward different types of research within the field. They also noted, however, that advocates, toxicologists, and animal modelers are often not included on standing study sections associated with the NIH Center for Scientific Review. An intermediate-term metric might thus include how representation on study sections have changed and whether more advocates are included in study sections. Another Committee member suggested establishing or strengthening standing study sections that review animal and human research. Yet another suggested that the problem might not be how funds are distributed, but how applications are assigned to study sections.

Dr. Gould pointed out that the criteria for establishing a new study section are somewhat stringent, but that researchers can suggest reviewers to study sections or volunteer to serve. Committee members suggested publishing Requests for Information to identify experts in various disciplines related to environmental influences on breast cancer, or a website where investigators can post their areas of expertise. Such a directory could allow investigators interested in breast cancer and the environment to find potential collaborators and suggest potential reviewers to add to study sections. One model is a California program that is establishing a stable of qualified experts on particular topics. This program not only identifies potential experts, but also evaluates them for suitability. BCERP also was cited as a model that encourages connections with clinical and epidemiological researchers.

Changes in how awards are distributed across funding mechanisms were also suggested as an intermediate metric. However, this suggestion sparked debate about the balance between investigator-initiated and directed research. Some Committee members advocated for more focused research to address existing gaps in the field of breast cancer and the environment, and some even suggested moving away from R01s as the primary vehicle for allocating funds. However, several Committee members noted the importance of continuing to support all models of research, including investigator-initiated research and centers. They pointed out, for example, that centers can bring in advocates, facilitate multidisciplinary collaborations, and encourage the rapid translation and dissemination of new discoveries. Some members felt that moving away from R01s would be detrimental to the next generation of breast cancer researchers, and they described previous push-back from the research community at top-down, directed research. Others noted new types of R01s, such as the multidisciplinary R01s, that can encourage innovative research. The Committee thus suggested a metric in terms of the amount of directed funding that focuses on breast cancer and the environment, and it agreed to keep the focus on research dollars, rather than on specific mechanisms. The Committee further clarified that it is not necessarily calling for a move away from R01s; rather, it is emphasizing more directed research to address some of the gaps in research on breast cancer and the environment. The Committee also emphasized the need for transparency in how such research is reviewed. Drs. Portier and Forman referred to the funding model proposed by the RP as a potential mechanism to direct research toward gaps.

The Committee also agreed that the Intramural Program at NIH should not be overlooked. This Program has substantial resources and the flexibility to conduct high-risk research. However, Committee members cautioned that the Intramural Program should distinguish itself from the Extramural Program, rather than simply compete with R01-type research.

Dr. Forman also noted the need for more training in breast cancer and the environment to build the field and perhaps meet the criteria for new study sections. She and other Committee members acknowledged, however, that recruitment into environmental research is hampered by the perception that environmental research is difficult and offers few funding opportunities.

The Committee agreed on two long-term goals: prevention and finding definitive answers about suspected environmental exposures. Committee members clarified that prevention refers not only to prevention of recurrence, but also to prevention of the first diagnosis of cancer. They also emphasized that prevention should be considered as part of the cancer continuum. The degree of movement from the current paradigm focused on diagnosis and treatment to one focused on the cancer continuum was suggested as a long-term metric.

Dr. Walker noted that the introduction of the report should note the lack of progress in breast cancer, but that it should note environmental influences on breast cancer as a particular area where progress is lacking.

E. Overriding Environmental Issues

The IBCERCC reviewed and revised a draft definition of the environment and introductory comments on the environmental issues expected to be covered in the Committee report. The following paragraphs were proposed for the introduction of the report:

> The environment includes all of the surroundings of and influences on living organisms. The complexity of environmental influences on the risk of breast cancer highlights the challenges to research to unravel these relationships. This definition of the environment encompasses a wide range of types of external influences on breast cancer risk.
>
> The major types of environmental factors include:
>
> - Lifestyle and behavioral factors such as alcohol intake or physical activity.
> - Chemical agents such as through pesticides and industrial pollutants, consumer products, and medications.
> - Physical agents such as:
>   - Radiation from our environment or from medical sources;
>   - Metals and other physical substances; and
>   - Physical features of the environment such as walkable neighborhoods that may influence our physical activity levels.
> - Biological agents such as bacteria, parasites, and viruses.
> - Sociocultural influences, such as family, community, psychosocial, and social (e.g., socio-economic) and societal factors, that may determine exposures to, the extent of exposure, or ability to ameliorate the impact on chemical, physical, and lifestyle and behavioral factors that influence cancer risk.
>
> Personal susceptibility factors also affect breast cancer risk. These include our genetic make-up; certain genetic factors, such as some genetic variants and regions along our chromosomes have been implicated as well as rarer genetic variants that lead to a higher breast cancer risk. Epigenetic characteristics that are potentially heritable but do not involve changes in the genetic sequence have been implicated as the basis for parental characteristics that influence breast cancer risk. Many personal susceptibility factors are related to reproductive factors such as age at first birth. Other personal susceptibility factors implicated in breast

cancer risk include how well or poorly we metabolize or accumulate chemicals in our bodies as well as certain metabolic and physiologic processes such as inflammation and oxidative stress.

Other important features that are involved in breast cancer risk include:

- Breast cancer is itself a complex disease, and environmental factors have a role in the many different manifestations of this disease.
- The influence of human developmental factors such as age of exposure of environmental agents on risk of disease.
- Certain groups, such as children and the disadvantaged, tend to be more heavily exposed and have higher body burdens than others and such disparities may contribute to disparities in breast cancer risk.
- That some environmental factors may lead to a chain of events, such as mutations in genes, that in turn lead to cancer, whereas others may significantly influence the personal susceptibility factors that are intimately involved in influencing the process of carcinogenesis (the steps leading to cancer), such as an environmental chemical that increases inflammation.
- That multiple exposures and multiple human body reactions to those exposures are occurring at the same time and over time.

Some of these environmental factors and personal susceptibility factors are better understood than others. One area that is poorly understood is whether and how physical and chemical factors, as well as lifestyle and behavior, might increase risk for breast cancer in humans. These major types of environmental exposures are the focus of this report.

Rapid progress in this area is needed because:

- There have been a wide range of chemical exposures, either naturally forming or man made, that have been implicated as factors in breast cancer risk through animal and human studies, and the general public is concerned about them.
- Exposures are common in the general population.
- The nature of exposures creates complex challenges (e.g., the tradeoff between medical radiation and subsequent breast cancer risk; the regulation of chemicals).
- Evidence suggests that children have higher exposures than adults.
- Scientific progress has been slow, and more innovative approaches are needed to make faster and more definitive progress.

This draft will be sent to Committee members for further editing.

F. Cross-cutting Themes

On the second day of the meeting, the Committee raised the following issues, which cut across all three Subcommittees:

- The complexity of environmental influences on breast cancer, which for example raises questions about new ways of supporting and conducting research.
- The proportion of breast cancer attributable to the environment, and the need to study gene-environment interactions. The Committee noted here that the report is more likely to state that the proportion of breast cancer cases attributable to environmental factors is higher than that associated with genetics, rather than state a specific percentage. Committee members

also pointed out that the exact percentage is unknown because of the uncertainty of estimation and the complexity of the problem.

- The per-person and total economic cost of breast cancer and potential savings by addressing environmental factors and ultimately, improving prevention.
- Breast cancer as a global epidemic, with increasing risks associated with environmental influences.
- The need for more interagency coordination of research and communication of research results.
- The need to shift the research paradigm from a focus on diagnosis, treatment, and survival to one focused on prevention, especially primary prevention.
- The need to validate animal model studies and better explain the relevance of these models to human health.
- The need for a systems biology approach in studying breast cancer and the environment.
- The need for education and outreach to increase awareness and overcome silo effects across agencies, institutions, research disciplines, sectors, and even within the breast cancer research community. Increased awareness can facilitate the formation of public-private partnerships, for example.
- An improved balance between a reductionist and integrative research approach, and the need for more collaboration.
- The involvement of advocates, consumers, community members, and other stakeholders in studies, the research process, and study sections.

The introduction of the report could also note that it is not just breast cancer that is affected by the government. Several issues discussed by the Committee, for example life course research, are also applicable to other cancers and to other diseases and conditions such as asthma, obesity, infertility, and autism.

Committee members also noted a lack of research, other than that focused on some lifestyle factors, on environmental influences on survival and quality of life in patients already diagnosed with cancer. The SOS will explore this issue further.

V. SUBCOMMITTEE BREAKOUT REPORTS

By the end of the meeting, each Subcommittee was charged with coming up with final headings and table of contents for their chapters.

A. State-of-the-Science Subcommittee

Dr. Haslam reported that the SOS first discussed the overall introduction, which will begin by discussing trends in breast cancer statistics, known risk factors, known mechanisms of tumor development, and funding that has been devoted to research in breast cancer. The introduction will then discuss the state of the science, specifically:

- Breast development over the life span.

- Carcinogenesis, including mutational and promotional events.
- Advances in prevention, diagnosis, and treatment.

The advances section will cover research from 1972 forward and will focus on advances from federally funded research. The SOS will poll members of the IBCERCC for their opinions on significant advances; obtain information from NIH and DoD, the major sources of federal funding in breast cancer research; and possibly conduct literature reviews. These tasks are expected to be completed by mid-July 2011.

The next section of the chapter will focus on the state of the science for animal and human studies, with a short summary, conclusions, and research gaps. This section will be followed by a section on moving forward, with recommendations.

On Day 2 of the meeting, Ms. McGuinn reported that the SOS refined its outline such that the Subcommittee introduction will now start with a discussion of breast cancer development over the life span and a discussion of the life course, then move to carcinogenesis, population heterogeneity in genetic susceptibility, and advances in breast cancer prevention, diagnosis, and treatment. The second section of the chapter will focus on the state of the science and research gaps in animal studies, and the third section of the chapter will focus on the same for human studies. The chapter will end with a discussion of emerging areas, with a table on future directions in animal and human research, a list of key research needs, and a discussion on paradigms in human and animal studies. Ms. McGuinn, Dr. Forman, Dr. Winn, and Dr. Ambrosone will explore the epidemiological literature; Dr. Sathyamoorthy and Ms. Barlow will work on advances; and Drs. Fenton and Haslam will focus on animal studies.

Discussion

A Subcommittee member noted that during previous phone calls, the Subcommittee had also discussed a section on the difficulties associated with assessing environmental exposures. Such difficulties arise from misclassifications, from people moving from place to place, and from people not knowing about their exposures.

B. Research Process Subcommittee

Dr. Gould reported that the RP decided to place the portfolio analysis chapter after the chapter on research models because Subcommittee members felt that portfolio analysis should examine both research topics and funding mechanisms.

The Subcommittee then spent the bulk of its time discussing a chapter devoted to funding models. This chapter will discuss existing and widely used models, emerging and innovative models, and recommended models to support research on breast cancer and the environment. The Subcommittee agreed that new research funding models are needed for breast cancer and the environment, because this field represents a complex problem that will not be addressed adequately by traditional reductionist approaches. The Subcommittee further agreed that new tools are needed to quantitatively integrate reductionist approaches and that new funding models should address the needs of all stakeholders addressing breast cancer and the environment.

The RP thus proposed a research funding model that employs a systems approach to address the complex mixtures of chemicals, behavior, and lifestyle; complex genetics and their interactions with chemicals, behavior, and lifestyle; and the complexity of life stages and windows of susceptibility. The systems approach will cover all levels, from the molecular through the population. The Subcommittee proposes a stepwise process in which a qualitative approach will be used first to develop a conceptual framework, then a quantitative approach will be used to parameterize the framework. The systems approach is expected to be interdisciplinary, collaborative, testable, open to validation, and conceptually coherent. The Subcommittee also proposed that the approach operate similarly to Wikipedia and thus be open source and transparent. In addition, the funding model is a living model that is tested and modified over the years. A mechanism is needed to regularly evaluate the state, challenges, and utility of the model. The Subcommittee felt that this funding approach could help investigators visualize linkages among the complex factors underlying breast cancer and the environment, identify and prioritize gaps, and identify the most efficient nodes for intervention.

Other funding models discussed during the breakout session included the Innovator/Howard Hughes model, in which a leader in any field is given funding to address a scientific question; the challenge.gov model, in which questions are posted and investigators compete for an award to address the question; and the NSF Ideas Lab model.

On the second day, Dr. Portier reported that the RP refined the organization and terminology of its sections. The first chapter will focus on funding *mechanisms* (not *models*). It will first discuss classic funding mechanisms, then move to new and emerging mechanisms. The chapter will note how these funding mechanisms reflect the goals and responsibilities of various NIH Institutes, and how by using these mechanisms, the Institutes are fulfilling the missions authorized by Congress. However, research on breast cancer and the environment will require these Institutes and other agencies to consider areas once dismissed as low priorities or the responsibilities of other Institutes or agencies.

The second chapter will focus on portfolio analysis. It will explore the allocation of research funding into major science categories, from a global point of view, and link to the first chapter on funding mechanisms. The chapter also will discuss the ability of the current coding system to help stakeholders understand whether progress has been made, and it will further explore the need for accurate coding to identify gaps and overlaps in funding. In this chapter, the RP will recommend improved specificity, as well as shared coding across systems or a common coding system. Such a system can assist with the metrics of evaluation.

As discussed during the previous day, the third chapter will focus on the RP's proposal for a framework focused on breast cancer and the environment. Dr. Portier reminded the Committee that a framework is needed to determine how individual research efforts have added to a global knowledge of breast cancer, with an ultimate goal of prevention. The framework should help researchers envision and map out parts of the landscape in breast cancer and the environment, to foster prioritization and decision making. Thus, the framework can help with the identification of gaps and opportunities, possibly stratified by individual agencies' areas of responsibility. The RP proposes that the framework be open, inclusive, and integrative, and the Subcommittee envisions that the framework will help in directing research toward gaps and opportunities. The Subcommittee also expects that such a framework will be amenable to both team and individual

research efforts and that it will allow agencies to bring their infrastructure and intellectual capital, including those agencies not focused specifically on breast cancer. For example, the U.S. Department of Agriculture might have infrastructure or research that could add to the global knowledge about breast cancer and the environment. The RP suggests that the National Academy of Sciences could be tasked with developing this framework.

The third chapter also will make recommendations on using existing funding mechanisms to foster innovation. The Howard Hughes Key Investigator mechanism, which identifies individuals at key stages in their careers and provides them with flexible funding and the infrastructure and incentives to be creative, was cited as a model for this type of approach.

Discussion

Dr. Gould agreed with IBCERCC members who pointed out that models do not have to be right to be useful. However, he noted that in the future, the models will have to be right if they are used as a basis for intervention. He and other RP members discussed existing funding models such as the NCI Cancer Intervention and Surveillance Modeling Network, which work at the epidemiological level but include no information on biological mechanisms at the tissue, cellular, and molecular levels. One RP member clarified that the funding model envisioned by the Subcommittee would involve people from a variety of government, academic, and industrial agencies to determine how best to frame a problem and map its pieces. Such a model would draw from the existing resources and infrastructure of various agencies, generate several hypotheses, and support research projects with various parts. The model would be open source and data shared so that all pieces of the science would be available to the entire consortium, as well as to the entire scientific community, who can add other discoveries. In the proposed funding model, multiple funding mechanisms might be added over the life of the framework to facilitate different dynamics in filling out the map.

One IBCERCC member pointed out that a similar approach had been used in developing the National Children's Study (NCS), which might offer helpful lessons. The NCS now has 22 hypotheses, and researchers have been working on the NCS framework for years. An RP member emphasized that the novel component of the proposed funding model is the requirement for it to be open source and living. The RP envisions pulling investigators together and building the funding model as an interagency, cross-university, cross-partnership endeavor, rather than having investigators compete to put forward the best model.

IBCERCC members also expressed concern that the model focused too much on an R01-type approach. However, RP members clarified that the model also could include prevention and intervention studies.

After the second day's breakout session, Committee members felt that the RP's framework proposal was clearer and agreed with it. In response to questions, Dr. Portier clarified that the Subcommittee did discuss how the advocacy community would be involved in development of the framework and expected that the framework would be open to all stakeholders, not just researchers. Dr. Portier reiterated that the RP also proposed that the framework be reviewed and priorities set on a regular basis. He added that a structure similar to the proposed framework is already used by the European community.

One Committee member commented that because this report will go to Congress, it should adopt a positive tone about previous and existing federal research support and the work that has already been done. She stressed that the report should note that while much work has been done, more work is needed to clarify what is known and what remains undetermined. The report should also note the shifting focus from diagnosis and treatment to prevention. Dr. Portier noted that without the research that has been done so far, the framework proposed by the RP would not be possible.

C. Research Translation, Dissemination, and Policy Implications Subcommittee

Dr. Zahm reported that the RTDPI discussed definitions, outlines for two major sections, and issues it felt the other Subcommittees should include. The RTDPI has shortened their sections by presenting the principles of best models and practices and by moving examples to an appendix.

Dr. Zahm noted that some issues raised by the Subcommittee were discussed in Dr. Haslam's presentation. She acknowledged that prevention, epidemiological, and clinical studies could be added to the funding model presented by Dr. Gould, but she also encouraged the RP to consider the models agencies use to include communities and stakeholders in their research. The RP model proposes to address the needs of stakeholders, but Dr. Zahm emphasized the need to include stakeholders in the actual process or conduct of research. The RTDPI also emphasized the need for training, which is often ignored during times of tight budgets but could help community members and stakeholders contribute to research. In addition, the problem of fragmentation and overlap across agencies is a theme that could be addressed by all three Subcommittees and by a call for interagency coordination. Dr. Zahm concluded her presentation by noting that the research community should push for resources to support research on breast cancer and the environment even in this time of tight budgets.

During its breakout discussions on the second day, the RTDPI emphasized radical recommendations. The Subcommittee refined its definitions of translation and dissemination and will send them to Committee members for feedback. The Subcommittee also refined its chapter outlines. The RTDPI's first chapter, which will focus on translation, will discuss the essential translation components that are applicable to research on breast cancer and the environment, and it will present case studies and the strengths, weaknesses, opportunities, and challenges associated with existing models. This presentation most likely will be a matrix, followed by two or more paragraphs and the Subcommittee's radical recommendations.

The Subcommittee also noted the importance of integrating capacity-building grants into public-private partnerships and discussed models that allowed the dissemination of information early in the research process. The RTDPI also discussed the timing of communication, for example how to balance the research team's possible desire to hold information for publication or programmatic purposes against the desire of research participants or other members of the affected community to have that information sooner.

Discussion

In response to questions from Committee members, Dr. Zahm provided examples of fragmentation and overlap. In one example, one agency might regulate a particular exposure that comes from the air or water, whereas another agency might regulate it because it comes from a drug or cosmetic. In another example, NIH might conduct research on an exposure or preventive

action, but another agency will carry out the public health implementation of findings from that research. Each agency might communicate about the same topic in a different way. Some efforts are under way to establish interagency groups to explore issues such as autism or fluoride in the drinking water, and these groups are developing common messages.

On the second day, in response to questions, RTDPI members clarified that the Subcommittee also discussed the ethical issues around the communication of science. One such issue is patient confidentiality. Another is the need for the community and researchers to work together in deciding how to disseminate information that affects the community.

Dr. Forman observed that when science is ready for translation into public health practice is a common theme across Subcommittees and chapters. RP members suggested that its proposed framework could help stakeholders establish standards to determine when a research finding might have a public health impact. The SOS also has discussed how to determine when research findings have reached the point where action is needed. The Committee agreed that researchers, advocates, and other stakeholders should discuss this issue at the beginning of a research project.

Dr. Forman pointed out that although some elements of each Subcommittee's introduction might be incorporated into the overall introduction of the report, there should still be an introduction to each chapter because it will frame the discussion from a specific perspective.

VI. GROUP DISCUSSION: OVERARCHING GOALS

The IBCERCC spent this time highlighting overarching goals to which its recommendations will be aimed. These goals will be discussed in the report's introduction, along with short-, intermediate-, and long-term goals and associated metrics.

- To provide usable data and information for multiple audiences to use to improve health.
- To prevent breast cancer incidence by identifying the earliest steps in breast cancer risk.
- To find definitive answers to whether suspected environmental factors influence breast cancer risk.
- To keep the public informed and active in this area of research by harmonizing the roles of advocacy and science.
- To clarify the risk factors within an individual's control and emphasize that most environmental factors are beyond that individual's control, to avoid "blaming the patient" for his or her cancer diagnosis.
- To create an infrastructure to foster innovation in research, funding mechanisms, and how research is directed toward the goal of prevention.
- To emphasize the role of Federal agencies in inspiring private and nonprofit investment and participation in research on breast cancer and the environment.
- To work with other organizations, such as the Breast Cancer Research Foundation or the Health Research Alliance, in conducting portfolio analysis across agencies.

- To direct research with the end user in mind, defining the end user broadly, such that the solutions yielded from research is what individuals, patients, physicians, providers, regulators, and other researchers need.
- Ultimately, to reduce the economic burden associated with breast cancer, both globally and at the individual level, thus providing a return on the public's investment in this research.

The Committee also agreed that the report should include one or two sentences reflecting that breast cancer is not the only disease influenced by environmental triggers. The report could suggest that increased support of research on breast cancer and the environment could open avenues to increase understanding of the effects of environmental exposures on other diseases. The report can also cite concern and interest at the national and international levels, as illustrated by reports from the President's Cancer Panel, the World Health Organization, and the CDC.

VII. OTHER BUSINESS

A. Timeline

The Committee agreed to have first drafts of all chapters ready by the September meeting of the IBCERCC. A schedule of Subcommittee and Committee meetings has been published; Subcommittees were asked to notify NIH if this schedule should be revised.

B. External Consultants

Dr. Forman suggested inviting Dr. Margaret Kripke, who will Chair the President's Panel on Prevention, as well as researchers conducting cutting-edge research to speak with Subcommittees to provide further information about progress to date. However, the Committee agreed that, in light of the short timeline for generating first drafts, these types of discussions should wait until after the drafts have been submitted. However, Committee members also suggested that Subcommittees could bring in consultants to inform their own discussions as they work on their chapter drafts.

VIII. ADJOURNMENT

The meeting adjourned at 4:15 p.m. on May 13, 2011.

CERTIFICATION

I hereby certify that, to the best of my knowledge, the foregoing minutes and attachments are accurate and complete.

/Michele Forman/
Michele Forman, PhD
Chairperson
Interagency Breast Cancer & Environmental Research Coordinating Committee

/Gwen W. Collman/
Gwen W. Collman, PhD

Executive Secretary
Research Process Subcommittee
Interagency Breast Cancer & Environmental Research Coordinating Committee

Proper signatures
Treat as signed, § 1.4(d)(2)